```
=>

---Logging off of STN---



=>
Executing the logoff script...


=> LOG Y

COST IN U.S. DOLLARS                              SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    36.23     203.38

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)        SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -5.25      -5.25

STN INTERNATIONAL LOGOFF AT 10:22:51 ON 24 APR 2006
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10/542,724 YONG CHU 4-24-2006

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$%^STN;HighlightOn=;HighlightOff=;

Connecting via Winsock to STN



Welcome to STN International!  Enter x:x

LOGINID:ssptaylc1626

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2


* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2          "Ask CAS" for self-help around the clock
 NEWS  3  DEC 23  New IPC8 SEARCH, DISPLAY, and SELECT fields in USPATFULL/
                  USPAT2
 NEWS  4  JAN 13  IPC 8 searching in IFIPAT, IFIUDB, and IFICDB
 NEWS  5  JAN 13  New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to
                  INPADOC
 NEWS  6  JAN 17  Pre-1988 INPI data added to MARPAT
 NEWS  7  JAN 17  IPC 8 in the WPI family of databases including WPIFV
 NEWS  8  JAN 30  Saved answer limit increased
 NEWS  9  FEB 21  STN AnaVist, Version 1.1, lets you share your STN AnaVist
                  visualization results
 NEWS 10  FEB 22  The IPC thesaurus added to additional patent databases on STN
 NEWS 11  FEB 22  Updates in EPFULL; IPC 8 enhancements added
 NEWS 12  FEB 27  New STN AnaVist pricing effective March 1, 2006
 NEWS 13  FEB 28  MEDLINE/LMEDLINE reload improves functionality
 NEWS 14  FEB 28  TOXCENTER reloaded with enhancements
 NEWS 15  FEB 28  REGISTRY/ZREGISTRY enhanced with more experimental spectral
                  property data
 NEWS 16  MAR 01  INSPEC reloaded and enhanced
 NEWS 17  MAR 03  Updates in PATDPA; addition of IPC 8 data without attributes
 NEWS 18  MAR 08  X.25 communication option no longer available after June 2006
 NEWS 19  MAR 22  EMBASE is now updated on a daily basis
 NEWS 20  APR 03  New IPC 8 fields and IPC thesaurus added to PATDPAFULL
 NEWS 21  APR 03  Bibliographic data updates resume; new IPC 8 fields and IPC
                  thesaurus added in PCTFULL
 NEWS 22  APR 04  STN AnaVist $500 visualization usage credit offered
 NEWS 23  APR 12  LINSPEC, learning database for INSPEC, reloaded and enhanced
 NEWS 24  APR 12  Improved structure highlighting in FQHIT and QHIT display
                  in MARPAT
 NEWS 25  APR 12  Derwent World Patents Index to be reloaded and enhanced during
                  second quarter; strategies may be affected

 NEWS EXPRESS  FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a,
               CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005.
               V8.0 AND V8.01 USERS CAN OBTAIN THE UPGRADE TO V8.01a AT
               http://download.cas.org/express/v8.0-Discover/

 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS LOGIN    Welcome Banner and News Items
 NEWS IPC8     For general information regarding STN implementation of IPC 8

Enter NEWS followed by the item number or name to see news on that
specific topic.
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* * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 10:21:22 ON 24 APR 2006

=> file reg
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILE 'REGISTRY' ENTERED AT 10:21:37 ON 24 APR 2006
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Property values tagged with IC are from the ZIC/VINITI data file
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STRUCTURE FILE UPDATES:    21 APR 2006  HIGHEST RN 881539-69-1
DICTIONARY FILE UPDATES:   21 APR 2006  HIGHEST RN 881539-69-1

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TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

  Please note that search-term pricing does apply when
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*********************************************************************
*                                                                   *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,   *
* effective March 20, 2005.  A new display format, IDERL, is now    *
* available and contains the CA role and document type information. *
*                                                                   *
*********************************************************************

Structure search iteration limits have been increased.  See HELP SLIMITS
for details.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=>
Uploading C:\Program Files\Stnexp\Queries\10542724\10542724a.str
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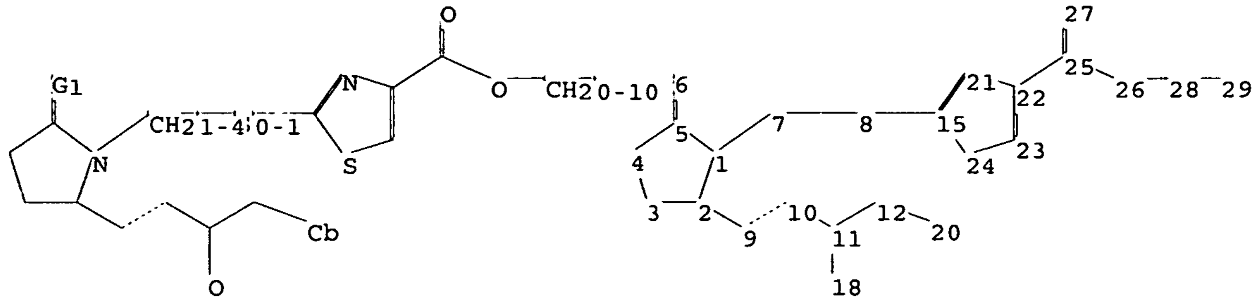


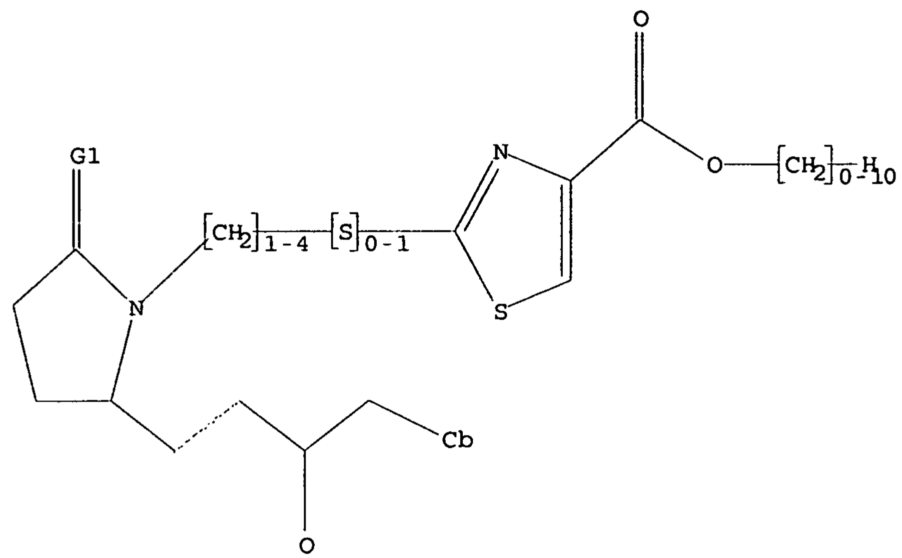
chain nodes :
6 7 8 9 10 11 12 18 20 25 26 27 28 29
ring nodes :
1 2 3 4 5 15 21 22 23 24
chain bonds :
1-7 2-9 5-6 7-8 8-15 9-10 10-11 11-12 11-18 12-20 22-25 25-26 25-27
26-28 28-29
ring bonds :
1-2 1-5 2-3 3-4 4-5 15-21 15-24 21-22 22-23 23-24
exact/norm bonds :
1-2 1-5 2-3 3-4 4-5 5-6 8-15 9-10 11-18 15-21 15-24 21-22 22-23 23-24
25-26 25-27
exact bonds :
1-7 2-9 7-8 10-11 11-12 12-20 22-25 26-28 28-29

G1:O,S

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:CLASS 7:CLASS 8:CLASS 9:CLASS
10:CLASS 11:CLASS 12:CLASS 15:CLASS 18:CLASS 20:Atom 21:Atom 22:Atom
23:Atom 24:Atom 25:CLASS 26:CLASS 27:CLASS 28:CLASS 29:CLASS

L1 STRUCTURE UPLOADED

=> d
L1 HAS NO ANSWERS
L1 STR



G1 O,S

Structure attributes must be viewed using STN Express query preparation.

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SAMPLE SEARCH INITIATED 10:22:04 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -       7 TO ITERATE

100.0% PROCESSED        7 ITERATIONS                              3 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE   **COMPLETE**
                        BATCH    **COMPLETE**
PROJECTED ITERATIONS:             7 TO      298
PROJECTED ANSWERS:                3 TO      163

L2            3 SEA SSS SAM L1

=> s l1 full
FULL SEARCH INITIATED 10:22:09 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -      91 TO ITERATE

100.0% PROCESSED       91 ITERATIONS                             40 ANSWERS
SEARCH TIME: 00.00.01

L3           40 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS                             SINCE FILE      TOTAL
                                                      ENTRY    SESSION
FULL ESTIMATED COST                                  166.94     167.15

FILE 'CAPLUS' ENTERED AT 10:22:19 ON 24 APR 2006
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FILE COVERS 1907 - 24 Apr 2006  VOL 144 ISS 18
FILE LAST UPDATED: 23 Apr 2006  (20060423/ED)

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=> s l3
L4            7 L3

=> d ibib abs hitstr tot
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L4 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2006:151237 CAPLUS
DOCUMENT NUMBER: 144:205827
TITLE: Preventive and/or remedy for hyperkalemia containing EP4 agonist
INVENTOR(S): Kuwahara, Atsukazu; Suzuki, Yuichi; Maruyama, Takayuki
PATENT ASSIGNEE(S): Ono Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 111 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006016695	A1	20060216	WO 2005-JP14885	20050809

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: JP 2004-232984 A 20040810

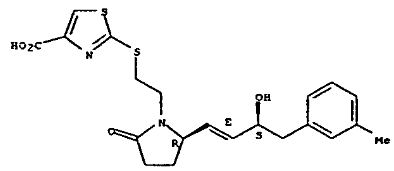
AB Disclosed is a preventive and/or remedy for hyperkalemia and a potassium excretion promoter containing an prostaglandin receptor EP4 agonist. Because of promoting potassium excretion, an EP4 agonist is useful as a preventive and/or remedy for hyperkalemia. A selective EP4 agonist is useful as a preventive and/or remedy for hyperkalemia having no side effect. Furthermore, an EP4 agonist is useful in ameliorating various symptoms of hyperkalemia (for example, sensation abnormality, error of perception, sense of exhaustion, muscle paralysis, nausea, vomiting, abdominal pain, diarrhea, arrhythmia, atrioventricular block, ventricular fibrillation, atrial fibrillation, asystole, respiratory arrest and/or respiratory distress and so on). For example, the EP4 agonistic effect of [(3-[[(1R,2S,3R)-3-hydroxy-2-[(1E,3S)-3-hydroxy-4-[3-(methoxymethyl)phenyl]but-1-enyl]-5-oxocyclopentyl]sulfanyl]propyl]sulfanyl]acetic acid (I) was in vitro examined. Also a tablet containing I 30 μg/tablet was formulated.

IT 494223-86-8 494223-92-6
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preventive and/or remedy for hyperkalemia containing EP4 agonist)

RN 494223-86-8 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[[2-[(2R)-2-[(1E,3S)-3-hydroxy-4-(3-methylphenyl)-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

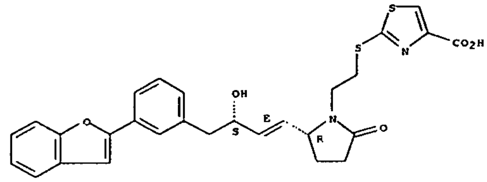
Absolute stereochemistry.
Double bond geometry as shown.

L4 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)



RN 494223-92-6 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[[2-[(2R)-2-[(1E,3S)-4-[3-(2-benzofuranyl)phenyl]-3-hydroxy-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2006:149115 CAPLUS
DOCUMENT NUMBER: 144:205819
TITLE: Preventive and/or remedy for lower urinary tract diseases containing EP4 agonist
INVENTOR(S): Okada, Hiroki; Maruyama, Takayuki
PATENT ASSIGNEE(S): Ono Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 119 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006016689	A1	20060216	WO 2005-JP14875	20050809

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: JP 2004-232985 A 20040810

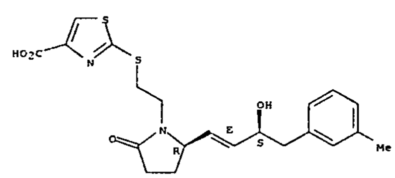
AB Disclosed are (1) a preventive and/or a remedy for lower urinary tract diseases such as inflammation in the lower urinary tract, cystitis (interstitial cystitis, etc.) and urethritis; (2) an agent for improving bladder compliance and/or bladder capacity; and (3) an agent for protecting bladder mucosa and/or bladder epithelial cells and/or promoting the regeneration thereof; each containing an EP4 agonist. An EP4 agonist is useful in ameliorating symptoms of lower urinary tract diseases such as (1) frequent urination, (2) urgency of urination, (3) pain in the reproductive organs and/or lower urinary tract (for example, bladder pain, urinary tract pain, vulvar pain, vaginal pain, scrotal pain, perineal pain, pelvic pain, etc.) and/or (4) unpleasantness in the reproductive organs and/or lower urinary tract. Among all, a selective EP4 agonist is useful as a preventive and/or remedy for lower urinary tract diseases having no side effect. For example, the effect of 4-[[2-[(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxybut-1-enyl]-5-oxopyrrolidin-1-yl]ethyl]sulfanyl]butanoic acid (I) in cystitis model rats was examined. Also, a tablet containing I 30 μg/tablet was formulated.

IT 494223-86-8 494223-92-6
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preventive and/or remedy for lower urinary tract diseases containing EP4 agonists)

RN 494223-86-8 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[[2-[(2R)-2-[(1E,3S)-3-hydroxy-4-(3-methylphenyl)-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

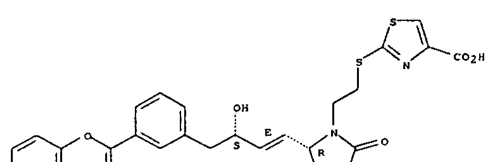
L4 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)

Absolute stereochemistry.
Double bond geometry as shown.



RN 494223-92-6 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[[2-[(2R)-2-[(1E,3S)-4-[3-(2-benzofuranyl)phenyl]-3-hydroxy-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

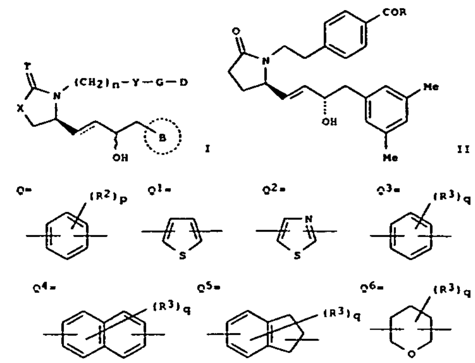
ACCESSION NUMBER: 2004:633912 CAPLUS
DOCUMENT NUMBER: 141:156958
TITLE: Preparation of 8-azaprostaglandin derivatives as prostaglandin EP4 receptor agonists
INVENTOR(S): Kambe, Tohru; Maruyama, Toru; Kobayashi, Kaoru; Tani, Kousuke; Nakai, Yoshihiko; Nagase, Toshihiko; Maruyama, Takayuki; Sakata, Kiyoto; Yoshida, Hideyuki; Fujimura, Shinsei; Nishiura, Akio; Abe, Nobutaka
PATENT ASSIGNEE(S): Ono Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 153 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004065365	A1	20040805	WO 2004-JP419	20040120
W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GH, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ				
JP 2005104836	A2	20050421	JP 2003-289954	20030808
EP 1586564	A1	20051019	EP 2004-703518	20040120
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
PRIORITY APPLN. INFO.:			JP 2003-11936 A	20030121
			JP 2003-289954 A	20030808
			WO 2004-JP419 W	20040120

OTHER SOURCE(S): MARPAT 141:156958

GI

L4 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)



AB Compds. having an 8-azaprostaglandin skeleton represented by the following general formula (I), salts thereof, solvates thereof, clathrate compds. thereof in cyclodextrin, or prodrugs thereof [wherein a solid line accompanied by a dotted line represents a single or double bond; a wavy line for the OH group represents an α- or β-disposition or a mixture with any α/β ratio thereof; D = C1-4 alkoxy-carbonyl, tetrazolyl; the ring A = Q, Q1, Q2; R2 = halo, C1-4 alkyl, C1-4 alkoxy; p = an integer of 0-4; Y = a bond, S; T = O, S; X = CH2, O, S; ring B = Q3, Q4, Q5, Q6; R3 = halo, each mono- to pentahalo-C1-4 alkyl or -C1-4 alkoxy, C1-4 alkoxy-C1-4 alkyl, Ph, each (un)substituted Ph or 3- to-13-membered bi- or tricyclic heterocyclyl containing 1-4 heteroatoms selected from N and S; q = an integer of 0-5] are prepared These compds. are prostaglandin EP4 receptor agonists and thereby useful in preventing and/or treating EP4-mediated diseases such as immune diseases, asthma, nerve cell death, arthritis, pulmonary injury, pulmonary fibrosis, pulmonary emphysema, bronchitis, chronic obstructive pulmonary disease, liver injury, acute hepatitis, nephritis, renal failure, hypertension, myocardial ischemia, systemic inflammatory reaction syndrome, sepsis, hemophagous syndrome, macrophage activation syndrome, Still's disease, Kawasaki's disease, burn, systemic granuloma, ulcerative colitis, Crohn's disease, hypercytokinemia in dialysis, multiorgan failure, shock and glaucoma. Because of having an effect of promoting osteogenesis, moreover, they are useful in preventing and/or treating diseases with bone loss (bone diseases such as primary osteoporosis, secondary osteoporosis, bone metastasis of cancer, hypercalcemia, Behcet's disease, bone defect and bone necrosis,

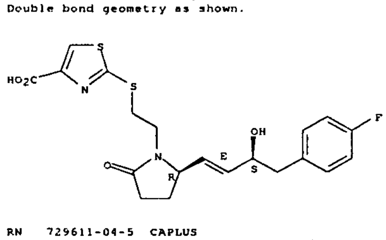
L4 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)

postoperative osteogenesis, alternative therapy for bone transplantation). Thus, (4R,5E,7S)-4-amino-7-hydroxy-8-(3,5-dimethylphenyl)oct-5-enoic acid Et ester hydrochloride (prepn. given) underwent reductive alkylation and cyclization with Me 4-formylmethylbenzoate using sodium triacetoxyborohydride in THF at room temp. overnight to give 2,3,4,5,17,18,19,20-octanor-8-azaprost-13-enoic acid Me ester deriv. (II; R = OMe) which was sapond. by a mixt. of 2 N aq. NaOH soln. and acidified with 2 N aq. HCl soln. to give II (R = OH). II (R = OH) showed the binding activity to prostaglandin EP4 receptor expressed by CHO cells with Ki of 6.4 nM. A tablet and vial formulation contg. a specific compd. I were described.

IT 494222-47-8P 729611-04-5P 729611-06-7P
729611-09-0P 729611-12-5P 729611-13-6P
729611-15-8P 729611-16-9P 729611-19-2P
729611-61-4P 729611-62-5P 729611-63-6P
729611-64-7P 729611-65-8P 729611-66-9P
729611-67-0P 729611-68-1P 729611-69-2P
729611-70-5P 729611-71-6P 729611-73-8P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 8-azaprostaglandin derivs. as prostaglandin EP4 receptor agonists or osteogenesis promoters for preventing and/or treating EP4-mediated diseases or bone diseases)

RN 494222-47-8 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[[2-[(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

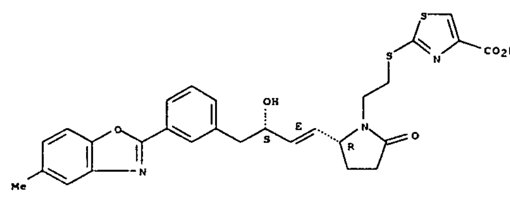
Absolute stereochemistry.
Double bond geometry as shown.



RN 729611-04-5 CAPLUS
CN 4-Thiazolecarboxylic acid,
2-[[2-[(2R)-2-[(1E,3S)-3-hydroxy-4-[3-(5-methyl-2-benzoxazolyl)phenyl]-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

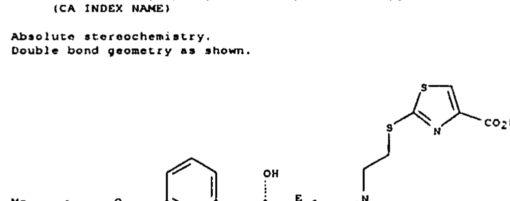
Absolute stereochemistry.
Double bond geometry as shown.

L4 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)



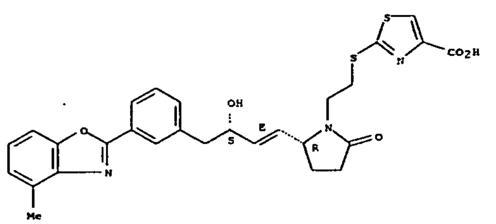
RN 729611-06-7 CAPLUS
CN 4-Thiazolecarboxylic acid,
2-[[2-[(2R)-2-[(1E,3S)-3-hydroxy-4-[3-(6-methyl-2-benzoxazolyl)phenyl]-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



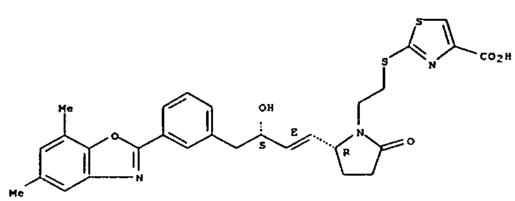
RN 729611-09-0 CAPLUS
CN 4-Thiazolecarboxylic acid,
2-[[2-[(2R)-2-[(1E,3S)-3-hydroxy-4-[3-(4-methyl-2-benzoxazolyl)phenyl]-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



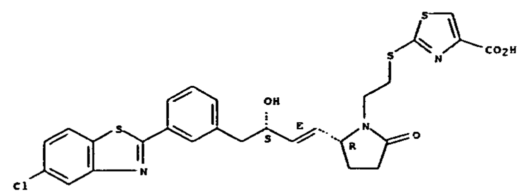
RN 729611-12-5 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[[2-[(2R)-2-[(1E,3S)-4-[3-(5,7-dimethyl-2-benzoxazolyl)phenyl]-3-hydroxy-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



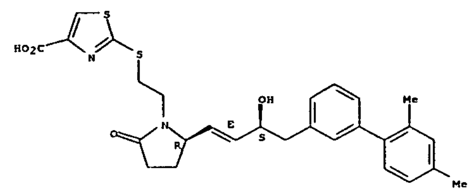
RN 729611-13-6 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[[2-[(2R)-2-[(1E,3S)-4-[3-(5-chloro-2-benzothiazolyl)phenyl]-3-hydroxy-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



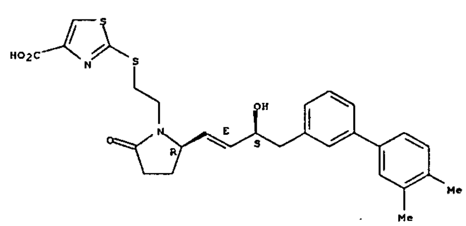
RN 729611-15-6 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[[2-[(2R)-2-[(1E,3S)-4-(2',4'-dimethyl[1,1'-biphenyl]-3-yl)-3-hydroxy-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



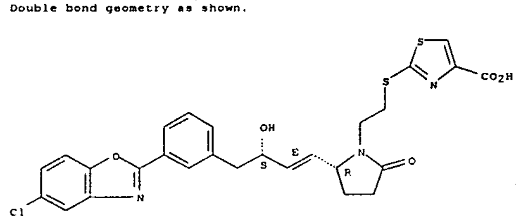
RN 729611-16-9 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[[2-[(2R)-2-[(1E,3S)-4-(3',4'-dimethyl[1,1'-biphenyl]-3-yl)-3-hydroxy-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



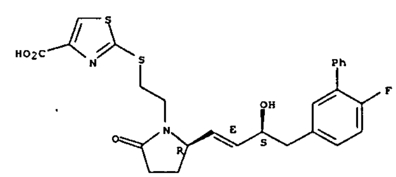
RN 729611-19-2 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[[2-[(2R)-2-[(1E,3S)-4-[3-(5-chloro-2-benzoxazolyl)phenyl]-3-hydroxy-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



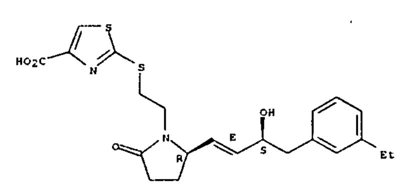
RN 729611-61-4 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[[2-[(2R)-2-[(1E,3S)-4-(6-fluoro[1,1'-biphenyl]-3-yl)-3-hydroxy-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



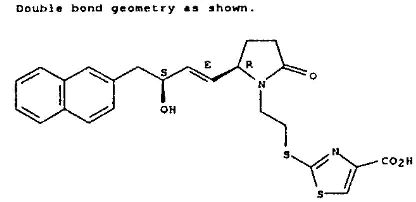
RN 729611-62-5 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[[2-[(2R)-2-[(1E,3S)-4-(3-ethylphenyl)-3-hydroxy-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 729611-63-6 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[[2-[(2R)-2-[(1E,3S)-3-hydroxy-4-(2-naphthalenyl)-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

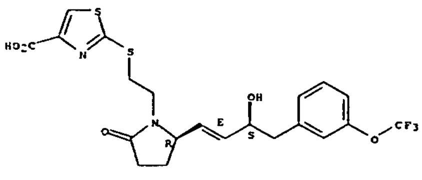
Absolute stereochemistry.
Double bond geometry as shown.



RN 729611-64-7 CAPLUS

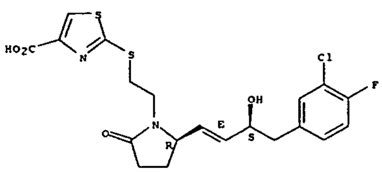
CN 4-Thiazolecarboxylic acid, 2-[[2-[(2R)-2-[(1E,3S)-3-hydroxy-4-[3-(trifluoromethoxy)phenyl]-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



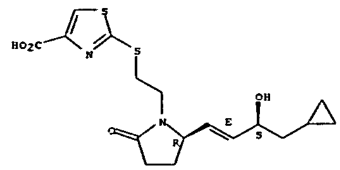
RN 729611-65-8 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[[2-[(2R)-2-[(1E,3S)-4-(3-chloro-4-fluorophenyl)-3-hydroxy-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



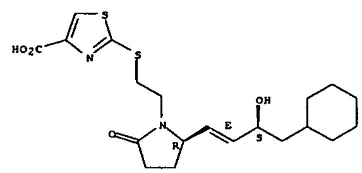
RN 729611-66-9 CAPLUS
CN 4-Thiazolecarboxylic acid,
2-[[2-[(2R)-2-[(1E,3S)-4-cyclopropyl-3-hydroxy-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



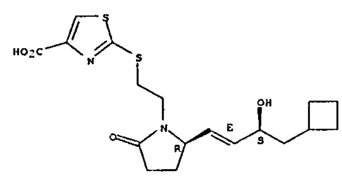
RN 729611-67-0 CAPLUS
CN 4-Thiazolecarboxylic acid,
2-[[2-[(2R)-2-[(1E,3S)-4-cyclohexyl-3-hydroxy-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 729611-68-1 CAPLUS
CN 4-Thiazolecarboxylic acid,
2-[[2-[(2R)-2-[(1E,3S)-4-cyclobutyl-3-hydroxy-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

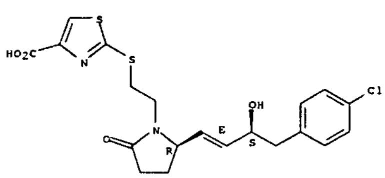
Absolute stereochemistry.
Double bond geometry as shown.



RN 729611-69-2 CAPLUS

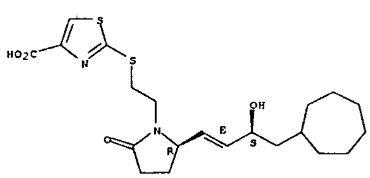
CN 4-Thiazolecarboxylic acid, 2-[[2-[(2R)-2-[(1E,3S)-4-(4-chlorophenyl)-3-hydroxy-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



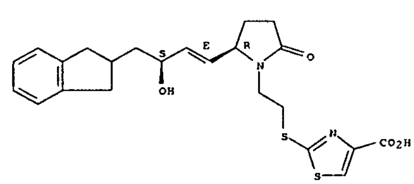
RN 729611-70-5 CAPLUS
CN 4-Thiazolecarboxylic acid,
2-[[2-[(2R)-2-[(1E,3S)-4-cycloheptyl-3-hydroxy-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



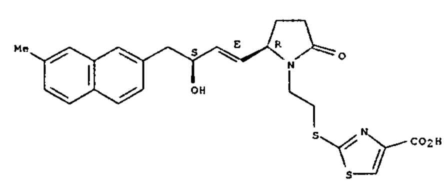
RN 729611-71-6 CAPLUS
CN 4-Thiazolecarboxylic acid,
2-[[2-[(2R)-2-[(1E,3S)-4-(2,3-dihydro-1H-inden-2-yl)-3-hydroxy-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 729611-73-8 CAPLUS
CN 4-Thiazolecarboxylic acid,
2-[[2-[(2R)-2-[(1E,3S)-3-hydroxy-4-(7-methyl-2-naphthalenyl)-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:370901 CAPLUS
DOCUMENT NUMBER: 140:391154
TITLE: A preparation of pyrrolidinone derivatives useful as selective EP4 receptor agonists
INVENTOR(S): Billot, Xavier; Beunard, Jean-Luc; Han, Yongxin; Young, Robert N.; Colucci, John; Girard, Mario; Wilson, Marie-Claire
PATENT ASSIGNEE(S): Merck Frosst Canada & Co., Can.
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004037786	A2	20040506	WO 2003-CA1620		20031023
WO 2004037786	A3	20040930			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
CA 2502914	AA	20040506	CA 2003-2502914		20031023
AU 2003275840	A1	20040513	AU 2003-275840		20031023
EP 1558602	A2	20050803	EP 2003-809227		20031023
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
JP 2006505572	T2	20060216	JP 2004-545645		20031023
PRIORITY APPLN. INFO.:			US 2002-421402P	P	20021025
			WO 2003-CA1620	W	20031023

OTHER SOURCE(S): MARPAT 140:391154
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to pyrrolidinone derivs. of formula I [wherein: Y1 = (CH2)2, CH:CH, 1,2-cyclopropanediyl; Y is C(O) or CH(OH); A is (CH2)1-4; Z = O, S, 1,2-cyclopropanediyl, HC:CH, C.tplbond.C, or a bond; Q is a disubstituted (hetero)aryl ring; W is a bond, unsubstituted C1-6 alkylene, or C1-6 alkylene substituted with 1-4 halogen atoms; R1 = OH, CN, CHO, etc.; R2 = C1-6alkyl, (CH2)0-6-(C6-10aryl), O-C1-10alkyl, etc.; R3 and R4 are independently selected from halogen, C1-6alkyl, or R3 and R4, together with the carbon atom to which they are attached, form a C3-7 cycloalkyl ring] useful as potent selective agonists of the EP4 subtype of

L4 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)

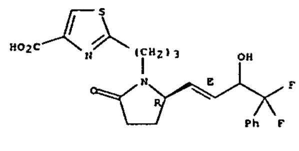
prostaglandin E2 receptors. The invention compds. are useful in treatment of glaucoma and other conditions which are related to the elevated intraocular pressure in the eye. The invention relates to the use of the invention compds. for mediating the bone modeling and remodeling processes of the osteoblasts and osteoclasts. The invention compds. were tested as EP4 agonists on intraocular pressure in rabbits and monkeys; prostanoid receptor binding assays and bone resorption assays were performed (in a subclass of the invented compds., agonists have EC50 values from 0.01 μM to 10 μM). The synthesized stereoisomeric pyrrolidinones II were prepd. from pyrrole deriv. III via oxidn., condensation with PhCF2C(O)CH2P(O)(OMe)2, keto-group redn. of the obtained unsatd. ketone IV, alc. protection, N-cleavage, addn. of thiophene deriv. V to the obtained compd. VI, sepn. of the isomers, alc. deprotection, and hydrolysis.

IT 685896-09-7P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyrrolidinone derivs. useful as selective EP4 receptor agonists)

RN 685896-09-7 CAPLUS

CN 4-Thiazolecarboxylic acid, 2-[3-[(2R)-2-[(1E)-4,4-difluoro-3-hydroxy-4-phenyl-1-butenyl]-5-oxo-1-pyrrolidinyl]propyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

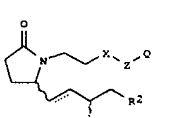


L4 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:757519 CAPLUS
DOCUMENT NUMBER: 139:276812
TITLE: Preparation of hydroxyorgano pyrrolidinones as EP4 receptor selective agonists for the treatment of hypertension and other disorders
INVENTOR(S): Cameron, Kimberly O'Keefe; Lefker, Bruce Allen; Knight, Delvin Roscoe, Jr.
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: PCT Int. Appl., 124 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2003077910	A1	20030925	WO 2003-IB844		20030306
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
CA 2478653	AA	20030925	CA 2003-2478653		20030306
AU 2003207900	A1	20030929	AU 2003-207900		20030306
EP 1487437	A1	20041222	EP 2003-704902		20030306
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
BR 2003008738	A	20050111	BR 2003-8738		20030306
JP 2005531516	T2	20051020	JP 2003-575963		20030306
US 2003207925	A1	20031106	US 2003-386307		20030311
PRIORITY APPLN. INFO.:			US 2002-365711P	P	20020318
			WO 2003-IB844	W	20030306

OTHER SOURCE(S): MARPAT 139:276812
GI



I

AB This invention is directed to hydroxyorgano pyrrolidinones (I; e.g. 4-[3-[2-(3-hydroxy-4-phenylbutyl)-5-oxopyrrolidin-1-yl]propyl]benzoic acid; R2, X, Z and Q are defined below and in more detail in the claims)

L4 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)

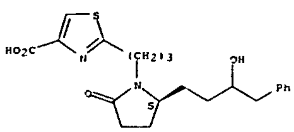
that are EP4 receptor selective prostaglandin agonists. This invention is also directed to pharmaceutical compns. contg. those compds. This invention is also directed to methods of treating hypertension, liver failure, loss of patency of the ductus arteriosus, glaucoma or ocular hypertension. IC50 values for binding of 5-[3-[2S-[3R-hydroxy-4-(3-trifluoromethylphenyl)butyl]-5-oxopyrrolidin-1-yl]propyl]thiophene-2-carboxylic acid (II) to various receptors are human EP1 receptor, >1000 nm; rat EP2 receptor, 463 nm; human EP3 receptor, > 1000 nm; and rat EP4 receptor, 11 nm. II exhibited an EC50 value of 0.6 nm in an assay involving cAMP elevation in 293S cell lines stably overexpressing recombinant rat EP4 receptors. Results are also presented for the hypotensive effect of the Na salt of II in in vivo rabbit and primate models. In I, a prodrug thereof, a pharmaceutically acceptable salt of said compd. or said prodrug or a stereoisomer or diastereomeric mixt. of said compd., prodrug or salt: the dotted line is a bond or no bond; X is -CH2- or O; Z is -(CH2)3-, thienyl, thiazolyl or Ph, provided that when X is O, then Z is phenyl; Q is carboxy, (C1-C4)alkoxycarbonyl or tetrazolyl;

R2 is -Ar or -Ar1-V-Ar2; V is a bond, -O-, -OCH2- or -CH2O-. Ar is a partially satd., fully satd. or fully unsatd. 5-8 membered ring optionally having 1-4 heteroatoms selected independently from O, S and N, or a bicyclic ring consisting of two fused independently partially satd., fully satd. or fully unsatd. 5-6 membered rings, taken independently, optionally having 1-4 heteroatoms selected independently from N, S and O, said partially or fully satd. ring or bicyclic ring optionally having 1-2 oxo groups substituted on C or 1-2 oxo groups substituted on S. Ar1 and Ar2 are each independently a partially satd., fully satd. or fully unsatd. 5-8 membered ring optionally having 1-4 heteroatoms selected independently from O, S and N, said partially or fully satd. ring optionally having 1-2 oxo groups substituted on C or 1-2 oxo groups substituted on S. Ar is optionally substituted on C or N, on one ring if the moiety is monocyclic, or on one or both rings if the moiety is bicyclic, with up to three substituents per ring each independently selected from hydroxy, halo, carboxy, (C1-C7) alkoxy, (C1-C4)alkoxy(C1-C4)alkyl, (C1-C7)alkyl, (C2-C7)alkenyl, (C3-C7)cycloalkyl, (C3-C7)cycloalkyl(C1-C4)alkyl, (C3-C7)cycloalkyl(C1-C4)alkanoyl, formyl, (C1-C8) alkanoyl, (C1-C6)alkanoyl(C1-C6)alkyl, (C1-C4)alkanoylamino, (C1-C4)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C1-C4)alkyl substituted aminocarbonylamino, sulfonamido, (C1-C4)alkylsulfonamido, amino, mono-N- or di-N,N-(C1-C4)alkylamino, carbamoyl, mono-N- or di-N,N-(C1-C4)alkylcarbamoyl, cyano, thiol, (C1-C6)alkylthio, (C1-C6)alkylsulfinyl, (C1-C4)alkylsulfonyl and mono-N- or di-N,N-(C1-C4)alkylaminosulfinyl, wherein said alkyl and alkoxy substituents in the definition of Ar are optionally substituted on C with up to three fluoro. Ar1 and Ar2 are independently optionally substituted on C or N with up to three substituents each independently selected from hydroxy, halo, carboxy, (C1-C7)alkoxy, (C1-C4)alkoxy(C1-C4)alkyl, (C1-C7)alkyl, (C2-C7)alkenyl, (C3-C7)cycloalkyl, (C3-C7)cycloalkyl(C1-C4)alkyl, (C3-C7)cycloalkyl(C1-C4)alkanoyl, formyl, (C1-C8)alkanoyl, (C1-C6)alkanoyl(C1-C6)alkyl, (C1-C4)alkanoylamino, (C1-C4)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C1-C4)alkyl substituted aminocarbonylamino, sulfonamido, (C1-C4)alkylsulfonamido, amino, mono-N- or di-N,N-(C1-C4)alkylamino,

L4 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)
carbamoyl, mono-N- or di-N,N-(C1-C4)alkylcarbamoyl, cyano, thiol, (C1-C6)alkylthio, (C1-C6)alkylsulfinyl, (C1-C4)alkylsulfonyl and mono-N- or di-N,N-(C1-C4)alkylaminosulfinyl, wherein said alkyl and alkoxy substituents in the definition of Ar1 and Ar2 are optionally substituted on C with up to three fluoro. (a) when X is (CH2)- and Z is -(CH2)3-, then R2 is not thienyl, Ph or Ph monosubstituted with chloro, fluoro, Ph, methoxy, trifluoromethyl or (C1-C4) alkyl; and (b) when X is (CH2)-, Z is -(CH2)3-, and Q is carboxy or (C1-C4) alkoxycarbonyl, then R2 is not (i) (C5-C7)cycloalkyl or (ii)phenyl, thienyl or furyl each of which may be optionally monosubstituted or disubstituted by one or two substituents selected, independently in the latter case, from halogen atoms, alkyl groups having 1-3 C atoms which may be substituted by one or more halogen atoms, and alkoxy groups having 1-4 C atoms. Although the methods of prepn. are not claimed, 41 example prepns. are included.

IT 431990-21-5P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(intermediate; preparation of hydroxyorgano pyrrolidinones as EP4
receptor
selective agonists for treatment of hypertension and other disorders)
RN 431990-21-5 CAPLUS
CN 4-Thiazolecarboxylic acid,
2-[3-[(2S)-2-(3-hydroxy-4-phenylbutyl)-5-oxo-1-pyrrolidinyl]propyl]- (9CI) (CA INDEX NAME)

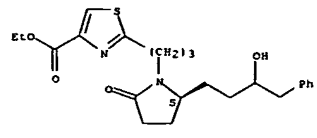
Absolute stereochemistry.



IT 431990-26-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of hydroxyorgano pyrrolidinones as EP4
receptor
selective agonists for treatment of hypertension and other disorders)
RN 431990-26-0 CAPLUS
CN 4-Thiazolecarboxylic acid,
2-[3-[(2S)-2-(3-hydroxy-4-phenylbutyl)-5-oxo-1-pyrrolidinyl]propyl]-, ethyl ester (9CI) (CA INDEX NAME)

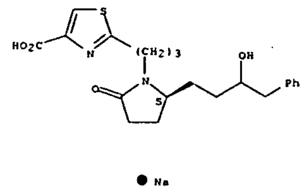
Absolute stereochemistry.

L4 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)



IT 431990-27-1P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of hydroxyorgano pyrrolidinones as EP4 receptor selective agonists for treatment of hypertension and other disorders)
RN 431990-27-1 CAPLUS
CN 4-Thiazolecarboxylic acid,
2-[3-[(2S)-2-(3-hydroxy-4-phenylbutyl)-5-oxo-1-pyrrolidinyl]propyl]-, monosodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

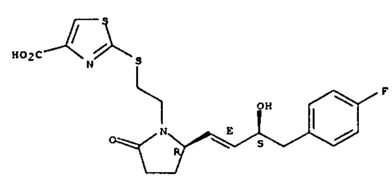
L4 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:97322 CAPLUS
DOCUMENT NUMBER: 138:142493
TITLE: Remedies for diseases with bone mass loss having EP4 agonist as the active ingredient
INVENTOR(S): Maruyama, Toru; Kobayashi, Kaoru; Kambe, Tohru; Maruyama, Takayuki; Yoshida, Hideyuki; Nishiura,
Akio;
Abe, Nobutaka
PATENT ASSIGNEE(S): Ono Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 474 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2003009872	A1	20030206	WO 2002-JP7385		20020722
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
CA 2454584	AA	20030206	CA 2002-2454584		20020722
EP 1417975	A1	20040512	EP 2002-747707		20020722
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK					
BR 2002011364	A	20040713	BR 2002-11364		20020722
ZA 2004000493	A	20050119	ZA 2004-493		20040122
US 2005020686	A1	20050127	US 2004-484500		20040122
NO 2004000331	A	20040323	NO 2004-331		20040123
PRIORITY APPLN. INFO.:			JP 2001-222148	A	20010723
			JP 2001-239895	A	20010807
			JP 2002-56449	A	20020301
			WO 2002-JP7385	W	20020722

OTHER SOURCE(S): MARPAT 138:142493
AB Disclosed are drugs for topical administration which contain an EP4 agonist as the active ingredient for preventing and/or treating diseases in association with bone mass loss. The EP4 agonists typified by
compds. with
the prostaglandin skeleton have an effect of promoting osteogenesis.
Thus, topical administration thereof is highly useful in preventing
and/or
treating diseases in association with bone mass loss, e.g., bone
diseases such
as primary osteoporosis, secondary osteoporosis, bone metastasis of cancer, hypercalcemia, Behcet's disease, bone loss and bone necrosis, postoperative osteogenesis, alternative therapy for bone transplantation. A compound (11α,15α,13E)-9-oxo-11,15-dihydroxy-16-(3-

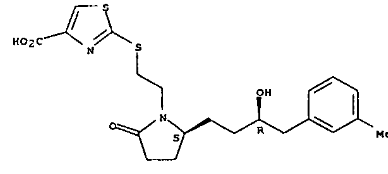
L4 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)
methoxymethylphenyl)-17,18,19,20-tetranor-5-thiaprost-13-enoic acid 2-nonanoyloxyethyl ester was prepd., and mixed with lactic acid-glycolic acid copolymer to obtain a microsphere. The obtained microsphere was administered to fracture bone part of a rat to examine the bone formation promoting effect.
IT 494222-47-8P 494223-71-1P 494223-74-4P
494223-85-7P 494223-86-8P 494223-90-4P
494223-91-5P 494223-92-6P 494224-07-6P
494224-08-7P 494224-09-8P 494224-13-4P
494224-14-5P 494224-15-6P 494224-18-9P
494224-19-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(remedies for diseases with bone mass loss containing prostaglandin
EP4
receptor agonists as active ingredients)
RN 494222-47-8 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[[2-[(2R)-2-[(1E,3S)-4-(4-fluorophenyl)-3-hydroxy-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



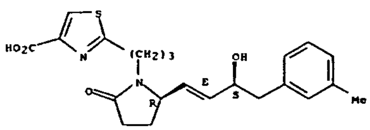
RN 494223-71-1 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[[2-[(2S)-2-[(3R)-3-hydroxy-4-(3-methylphenyl)butyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



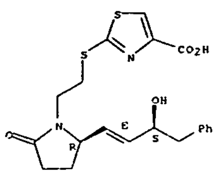
RN 494223-74-4 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[3-[(2R)-2-[(1E,3S)-3-hydroxy-4-(3-methylphenyl)-1-butenyl]-5-oxo-1-pyrrolidinyl]propyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



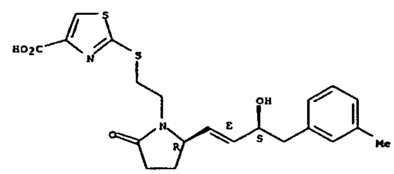
RN 494223-85-7 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[[2-[(2R)-2-[(1E,3S)-3-hydroxy-4-phenyl-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



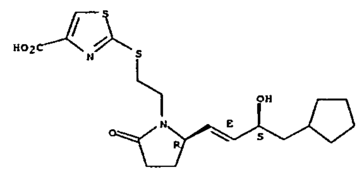
RN 494223-86-8 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[[2-[(2R)-2-[(1E,3S)-3-hydroxy-4-(3-methylphenyl)-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



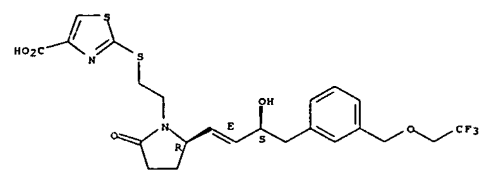
RN 494223-90-4 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[[2-[(2R)-2-[(1E,3S)-4-cyclopentyl-3-hydroxy-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



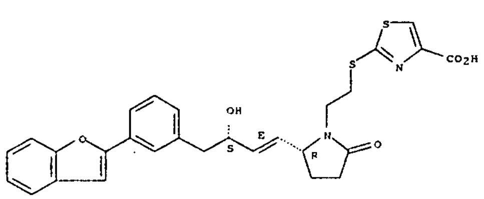
RN 494223-91-5 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[[2-[(2R)-2-[(1E,3S)-3-hydroxy-4-[3-[(2,2,2-trifluoroethoxy)methyl]phenyl]-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



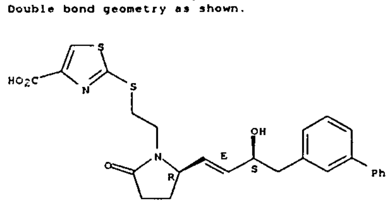
RN 494223-92-6 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[[2-[(2R)-2-[(1E,3S)-4-[3-(2-benzofuranyl)phenyl]-3-hydroxy-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



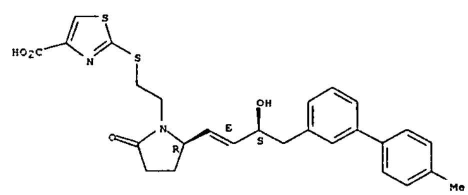
RN 494224-07-6 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[[2-[(2R)-2-[(1E,3S)-4-[1,1'-biphenyl]-3-yl-3-hydroxy-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



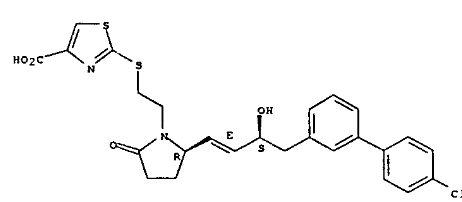
RN 494224-08-7 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[[2-[(2R)-2-[(1E,3S)-3-hydroxy-4-(4'-methyl[1,1'-biphenyl]-3-yl)-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



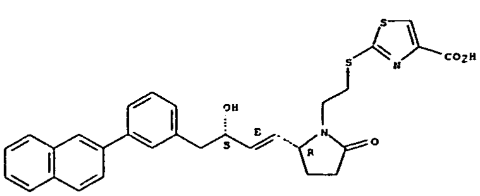
RN 494224-09-8 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[[2-[(2R)-2-[(1E,3S)-4-(4'-chloro[1,1'-biphenyl]-3-yl)-3-hydroxy-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



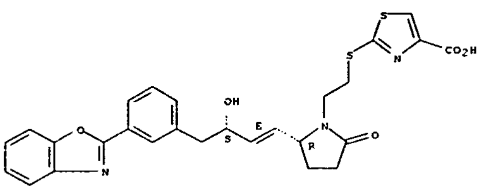
RN 494224-13-4 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[[2-[(2R)-2-[(1E,3S)-3-hydroxy-4-[3-(2-naphthalenyl)phenyl]-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 494224-14-5 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[[2-[(2R)-2-[(1E,3S)-4-[3-(2-benzoxazolyl)phenyl]-3-hydroxy-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

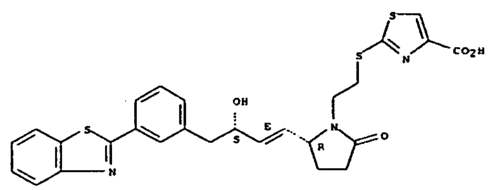
Absolute stereochemistry.
Double bond geometry as shown.



RN 494224-15-6 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[[2-[(2R)-2-[(1E,3S)-4-[3-(2-benzothiazolyl)phenyl]-3-hydroxy-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

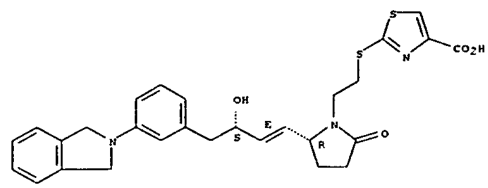
Absolute stereochemistry.
Double bond geometry as shown.

L4 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)



RN 494224-18-9 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[[2-[(2R)-2-[(1E,3S)-4-[3-(1,3-dihydro-2H-isoindol-2-yl)phenyl]-3-hydroxy-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

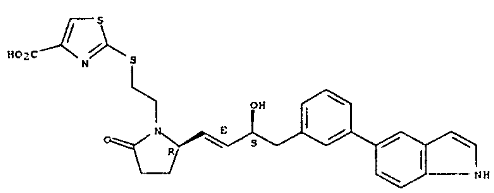
Absolute stereochemistry.
Double bond geometry as shown.



RN 494224-19-0 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[[2-[(2R)-2-[(1E,3S)-3-hydroxy-4-[3-(1H-indol-5-yl)phenyl]-1-butenyl]-5-oxo-1-pyrrolidinyl]ethyl]thio]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

L4 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN (Continued)



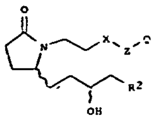
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:408643 CAPLUS
DOCUMENT NUMBER: 137:6083
TITLE: Preparation of EP4 receptor selective agonists for the treatment of osteoporosis
INVENTOR(S): Cameron, Kimberly O'Keefe; Lefker, Bruce Allen
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: PCT Int. Appl., 122 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002042268	A2	20020530	WO 2001-IB2073	20011105
WO 2002042268	A3	20020725		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2429850	AA	20020530	CA 2001-2429850	20011105
AU 2002010848	A5	20020603	AU 2002-10848	20011105
EP 1339678	A2	20030903	EP 2001-978757	20011105
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001015687	A	20030909	BR 2001-15687	20011105
EE 200300246	A	20031015	EE 2003-246	2Q011105
JP 2004521869	T2	20040722	JP 2002-544404	20011105
NZ 525164	A	20050429	NZ 2001-525164	20011105
US 2002065308	A1	20020530	US 2001-990556	20011121
US 6552067	B2	20030422		
US 2003149086	A1	20030807	US 2002-326366	20021220
US 6747054	B2	20040608		
BG 107697	A	20040130	BG 2003-107697	20030403
ZA 2003002803	A	20040413	ZA 2003-2803	20030410
NO 2003002360	A	20030723	NO 2003-2360	20030526
US 2004259921	A1	20041223	US 2003-668633	20030923
PRIORITY APPLN. INFO.:			US 2000-253275P	P 20001127
			WO 2001-IB2073	W 20011105
			US 2001-990556	A3 20011121
			US 2002-326366	A3 20021220

OTHER SOURCE(S): MARPAT 137:6083
GI



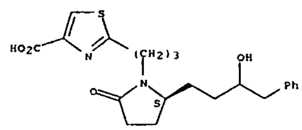
I

AB This invention is directed to EP4 receptor selective prostaglandin agonists I (e.g. 4-[3-[2-(3-hydroxy-4-phenylbutyl)-5-oxopyrrolidin-1-yl]propyl]benzoic acid), wherein R2, X, Z and Q are defined below and in more detail in the claims. This invention is also directed to pharmaceutical compns. containing those compds. This invention is also directed to methods of treating conditions which present with low bone mass, particularly osteoporosis, frailty, an osteoporotic fracture, a bone defect, childhood idiopathic bone loss, alveolar bone loss, mandibular bone loss, bone fracture, osteotomy, bone loss associated with periodontitis, or prosthetic ingrowth in a mammal comprising administering those compds. Although biol. testing protocols are included, no test results are given. In I, a prodrug thereof, a pharmaceutically acceptable salt of said compound or said prodrug or a stereoisomer or diastereomeric mixture of said compound, prodrug or salt: the dotted line is a bond or no bond; X is -CH2- or O; Z is -(CH2)3-, thienyl, thiazolyl or Ph, provided that when X is O, then Z is phenyl; Q is carboxy, (C1-C4)alkoxycarbonyl or tetrazolyl; R2 is -Ar or -Ar1-V-Ar2; V is a bond, -O-, -OCH2- or -CH2O-. Ar is a partially saturated, fully saturated or fully unsatd. 5-8 membered ring optionally having 1-4 heteroatoms selected independently from O, S and N, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsatd. 5-6 membered rings, taken independently, optionally having 1-4 heteroatoms selected independently from N, S and O, said partially or fully saturated ring or bicyclic ring optionally having 1-2 oxo groups substituted on C or 1-2 oxo groups substituted on S. Ar1 and Ar2 are each independently a partially saturated, fully saturated or fully unsatd. 5-8 membered ring optionally having 1-4 heteroatoms selected independently from O, S and N, said partially or fully saturated ring optionally having 1-2 oxo groups substituted on C or 1-2 oxo groups substituted on S. Ar is optionally substituted on C or N, on one ring if the moiety is monocyclic, or on one or both rings if the moiety is bicyclic, with up to three substituents per ring each independently selected from hydroxy, halo, carboxy, (C1-C7) alkoxy, (C1-C4)alkoxy(C1-C4)alkyl, (C1-C7)alkyl, (C2-C7)alkenyl, (C3-C7)cycloalkyl, (C3-C7)cycloalkyl(C1-C4)alkyl, (C3-C7)cycloalkyl(C1-C4)alkanoyl, formyl, (C1-C8) alkanoyl, (C1-C6)alkanoyl(C1-C6)alkyl, (C1-C4)alkanoylamino, (C1-C4)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C1-C4)alkyl substituted aminocarbonylamino, sulfonamido, (C1-

C4)alkylsulfonamido, amino, mono-N- or di-N,N-(C1-C4)alkylamino, carbamoyl, mono-N- or di-N,N-(C1-C4)alkylcarbamoyl, cyano, thiol, (C1-C6)alkylthio, (C1-C6)alkylsulfinyl, (C1-C4)alkylsulfonyl and mono-N- or di-N,N-(C1-C4)alkylaminosulfinyl, wherein said alkyl and alkoxy substituents in the definition of Ar are optionally substituted on C with up to three fluoro. Ar1 and Ar2 are independently optionally substituted on C or N with up to three substituents each independently selected from hydroxy, halo, carboxy, (C1-C7)alkoxy, (C1-C4)alkoxy(C1-C4)alkyl, (C1-C7)alkyl, (C2-C7)alkenyl, (C3-C7)cycloalkyl, (C3-C7)cycloalkyl(C1-C4)alkyl, (C3-C7)cycloalkyl(C1-C4)alkanoyl, formyl, (C1-C8)alkanoyl, (C1-C6)alkanoyl(C1-C6)alkyl, (C1-C4)alkanoylamino, (C1-C4)alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C1-C4)alkyl substituted aminocarbonylamino, sulfonamido, (C1-C4)alkylsulfonamido, amino, mono-N- or di-N,N-(C1-C4)alkylamino, carbamoyl, mono-N- or di-N,N-(C1-C4)alkylcarbamoyl, cyano, thiol, (C1-C6)alkylthio, (C1-C6)alkylsulfinyl, (C1-C4)alkylsulfonyl and mono-N- or di-N,N-(C1-C4)alkylaminosulfinyl, wherein said alkyl and alkoxy substituents in the definition of Ar1 and Ar2 are optionally substituted on C with up to three fluoro. (a) when X is (CH2)- and Z is -(CH2)3-, then R2 is not thienyl, Ph or Ph monosubstituted with chloro, fluoro, Ph, methoxy, trifluoromethyl or (C1-C4) alkyl; and (b) when X is (CH2)-, Z is -(CH2)3-, and Q is carboxy or (C1-C4) alkoxycarbonyl, then R2 is not (i) (C5-C7)cycloalkyl or (ii)phenyl, thienyl or furyl each of which may be optionally monosubstituted or disubstituted by one or two substituents selected, independently in the latter case, from halogen atoms, alkyl groups having 1-3 C atoms which may be substituted by one or more halogen atoms, and alkoxy groups having 1-4 C atoms. Although the methods of prepn. are not claimed, 41 example prepns. are included.

IT 431990-21-5P, 2-[3-[(2S)-(3-Hydroxy-4-phenylbutyl)-5-oxopyrrolidin-1-yl]propyl]thiazole-4-carboxylic acid
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(intermediate; preparation of EP4 receptor selective agonists for treatment of osteoporosis)
RN 431990-21-5 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[3-[(2S)-2-(3-hydroxy-4-phenylbutyl)-5-oxo-1-pyrrolidinyl]propyl]- (9CI) (CA INDEX NAME)

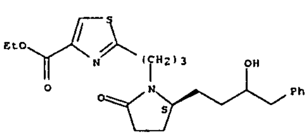
Absolute stereochemistry.



IT 431990-26-0P, 2-[3-[(2S)-(3-Hydroxy-4-phenylbutyl)-5-oxopyrrolidin-1-yl]propyl]thiazole-4-carboxylic acid ethyl ester
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of EP4 receptor selective agonists for treatment

of osteoporosis)
RN 431990-26-0 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[3-[(2S)-2-(3-hydroxy-4-phenylbutyl)-5-oxo-1-pyrrolidinyl]propyl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 431990-27-1P, Sodium salt of 2-[3-[(2S)-(3-hydroxy-4-phenylbutyl)-5-oxopyrrolidin-1-yl]propyl]thiazole-4-carboxylic acid
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of EP4 receptor selective agonists for treatment of osteoporosis)
RN 431990-27-1 CAPLUS
CN 4-Thiazolecarboxylic acid, 2-[3-[(2S)-2-(3-hydroxy-4-phenylbutyl)-5-oxo-1-pyrrolidinyl]propyl]-, monosodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.